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| EXAMINER | |
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| BRISTOL, LYNN ANNE | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/535,312 | JUNG ET AL. | |
| | Examiner | Art Unit | |
| | Lynn Bristol | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-15 are all the pending claims for this application.

2. The preliminary amendment of the specification filed on 6/5/06 has been entered.

### *Election/Restrictions*

3. Applicant's election of Group I (Claims 1-14) in the reply filed on 9/7/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claim 15 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/7/07.

5. Applicant's election without traverse of species for Ig constant region of SEQ ID NO: 29, heat-stable enterotoxin II E. coli-derived signal sequence, the heat-stable enterotoxin II of SEQ ID NO:36, the pSTIIdCG4Fc expression vector, and HMI0932 E. coli transformant in the reply filed on 9/7/07 is acknowledged. The Examiner has rejoined:

the heat-stable enterotoxin signal peptides of SEQ ID NOS:37-46,

the expression vectors pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIG4CHI_3, pSTIIG4Mo, and pSTIIG4H_K, and

the E. coli transformants (HMI0935), (HMI0927), (HMI0928), (HMI0929), (HMI0930), (HMI0936), (HMI0931), (HMI0933) and (HMI0934), with the corresponding elected species for examination.

6. Claims 1-14 are all the pending claims under examination.

***Oath/Declaration***

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either an application data sheet or supplemental oath or declaration.

***Specification***

8. The specification is objected to for the following reasons:

a) The specification fails to cross-reference the priority documents for this application.

b) The legends to Figures 1-5 on p. 9 of the specification do not provide sufficient description for each of the figures. For example, which E. coli transformants are

depicted in lanes 1-4 of Figure 1? Figure 2 shows 9 lanes but is not accompanied by a description of the lane contents. Figure 3 shows 5 lanes but is not accompanied by a description of the lane contents. Figure 4 shows C1q binding capacity of Ig Fc fragments but the y-axis is not identified. Figure 5 shows pharmacokinetic analysis of Fc conjugates but does not describe how this was performed or from where the sample was obtained.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-10, 12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-10, 12 and 14 are indefinite for the recitation "E. coli-derived signal sequence" in Claims 1 and 10, because the term "derived" does not have a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. Since it is unclear how the genus of E. coli signal peptide are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to the phrase. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass signal peptides with amio acid substitutions, insertions, or deletions, chemically derivatized molecules, or even mimetics. In the

absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine he metes and bounds of the claims.

b) Claims 2-5 are indefinite for the recitation "and combinations and hybrids thereof" in Claims 2 and 3, because the it is not clear how the constant regions from any one of the IgG, IgA, IgM, IgE or IgD isotypes can be combined into the nucleotide encoding the Ig constant region. Should the nucleotide encoding the Ig region comprise the different combinations of domains in-frame or in-tandem, and if so, could one of skill in the art expect any one of the constant domains to function fused to any other constant domain much less to a different isotype?

c) Claims 6 and 7 are indefinite for the recitation "the immunoglobulin region is composed of one to four domains selected from the groups consisting of CH1, CH2, CH3, CH4 and CL domains" in Claim 6, because it is not clear how the CL domain can be combined with any one to three of the CH1, CH2, CH3 or CH4 domains to make a constant region. Should the nucleotide encoding the Ig region comprise the different combinations of domains in-frame or in-tandem, and if so, could one of skill in the art expect a CL domain to function when fused to a CH domain?

d) Claim 12 is indefinite for the recitation "pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K" because the expression vectors are referred to by a laboratory designation and one of skill in the art could not determine the full nucleotide sequence or structure for any one of the separate vectors from the claim

or in reading the specification. Amending the claims to the recite the SEQ ID NO for each of the vectors would overcome the rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Biological Deposit Requirement***

10. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1) It is unclear if an expression vector, having the exact chemical identity of the expression vector pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K, is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of each the above vectors, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (a) the claimed vector; (b) a bacterial cell line which produces the chemically and functionally distinct vector claimed; and/or (c) the claimed vectors nucleic acid sequence is an unpredictable event.

2) The specification lacks deposit information for the deposit of the pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K vector. It is unclear whether vectors possessing the identical properties of this vector are known and publicly available or can be reproducibly isolated from nature without undue experimentation. With respect to the pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K vector, there is no indication in the specification that the vector is readily available to the public and the specification does not provide any guidance or direction to assist one skilled in the art to make and/or use the vectors. Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed vectors or cell lines reproducing the claimed vectors, a suitable deposit is required for patent purposes, evidence of public availability of the claimed vectors or cell lines reproducing the claimed vectors or evidence of the reproducibility without undue experimentation of the claimed vectors, is required.

If the deposit for the pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K expression vector is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by

an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed. Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

***Biological Deposit Requirement***

11. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is unclear if an E. coli transformant, having the exact chemical identity of the E. coli transformants, HMI0927, HMI0928, HMI0929, HMI0930, HMI0931, HMI0932, HMI0933, HMI0934, HMI0935, or HMI0936, is known and publicly available, or can be reproducibly isolated without undue experimentation. Copies of deposit receipts for the E. coli transformants, HMI0927, HMI0928, HMI0929, HMI0930, HMI0931, HMI0932,

HMI0933, HMI0934, and HMI0935, are provided at the end of the specification filed 5/17/05. No statement of assurances appears in the specification, and Applicants have not fileda declaration for biological deposit for any of the E. coli transformants.

*NO* deposit receipt appears for the E. coli transformant HMI0936. Therefore, a suitable deposit for patent purposes is suggested.

Without a publicly available deposit of each the above E. coli transformants, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (a) a bacterial cell line which produces the chemically and functionally distinct vector claimed; and/or (b) the claimed vectors nucleic acid sequence is an unpredictable event.

***Enablement***

12. Claims 2-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing Ig constant regions such as IgG, IgA, IgM, IgE and IgD, or IgG1, IgG2, IgG3 and IgG4, or CH1, CH2, CH3 and CH4, or CL, does not reasonably provide enablement for Ig constant regions that are combinations and hybrids of the foregoing constant regions, or comprising one to four domains of any one of CH1, CH2, CH3, CH4 and CL. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They

include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/Skill in the Art

Claims 2-7 are interpreted as being drawn to a method of producing an Ig constant region comprising transforming a prokaryotic cell with an expression vector including an E. coli derived signal sequence and a nucleotide sequence encoding an Ig constant region, culturing the transformant and isolating and purifying the Ig constant region where the Ig constant region is IgG, IgA, IgM, IgE, IgD and combinations and hybrids thereof (Claim 2), or IgG1, IgG2, IgG3, IgG4 and combinations and hybrids thereof (Claim 3), or the Ig constant region is an IgG4 constant region (Claim 4) or the Ig constant region is a human aglycosylated IgG4 constant region (Claim 5), or the Ig constant region is one to four domains of CH1, CH2, CH3, CH4 or CL (Claim 6), and the Ig constant region of Claim 6 further comprises a hinge region (Claim 7).

The relative skill in the art required to practice the invention is a molecular immunologist with a background in molecular biology and antibody chemistry.

Disclosure in the Specification

The specification does not provide a sufficient enabling description of the claimed invention. The disclosure appears to show only antibodies with certain specified amino acid substitutions. For example, the specification discloses expression vectors

encoding engineered Ig constant domains such as pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K. The instant claims encompass in their breadth any vector encoding any "combinations and hybrids" of a constant region from IgG, IgA, IgM, IgE, or IgD, or of a constant region of IgG1, IgG2, IgG3, IgG4, or of one to four domains of CH1, CH2, CH3, CH4 or CL.

Prior Art Status: Fc modifications

There does not appear to be sufficient guidance in the specification as field as to how the skilled artisan would make and use the claimed "combinations and hybrids thereof" or the "one to four domains...CH1, CH2, CH3, CH4 and CL." The state of the art at the time the invention was made recognized that even single amino acid differences can result in drastically altered function of antibodies. For example, Lund et al. (The Journal of Immunology 1996, 157:4963-4969) show that even a single amino acid replacement within the CH2 domain of IgG can alter the glycosylation profile of an antibody therefore influence its effector functions of Fc receptor binding and complement activation (see entire document, particularly Discussion on pages 4966-4968). Further, Lazar et al. (WO 03/074679) teach that the determinants of antibody properties, such as stability, solubility and affinity for antigen, important to its functions are overlapping; thus engineering an Fc region of an antibody may cause a loss in affinity for its antigen (see entire document, particularly page 3).

Given the extensive variation permitted by the instant claim language, the skilled artisan would not reasonably predict such "combinations and hybrids thereof" and the

combination of which "one to four domains of... CH1, CH2, CH3, CH4 and CL" have the same function as the instant claimed invention. Reasonable correlation must exist between the scope of the claims and scope to enablement set forth. Applicant does not appear to provide guidance as to other "combinations and hybrids thereof" or which if any combination of "one to four domains of... CH1, CH2, CH3, CH4 and CL" can be combined, and that meet all of the claimed limitations.

The specification does not appear to provide sufficient guidance as to which constant domains should or should not be changed to preserve any particular function. The variation permitted by the instant claim language is extensive. There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the claimed such "combinations and hybrids thereof" and the combination of which "one to four domains of... CH1, CH2, CH3, CH4 and CL." The specification provides no direction or guidance regarding how to produce such "combinations and hybrids thereof" and the combination of "one to four domains of... CH1, CH2, CH3, CH4 and CL" as broadly defined by the claims. In view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 1, 2, 6, 8, 10 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Adib-Conquy et al. (Protein Engineering 8:859-863 (1995); cited in the PTO 892 form of 8/7/07).

The interpretation of Claims 2 and 6 is discussed supra. The discussion of Claim 2 supra incorporates the interpretation of Claim 1. Claims 8, 10 and 14 are interpreted as being drawn to the method where the expression vector encodes a heavy chain and a light chain constant region (Claim 8), where the signal peptide is alkaline phosphatase or maltose binding protein (Claim 10) and the transformant is E. coli (Claim 14).

Abid-Conquy et al. describe a method for expressing a Fab fragment of a mouse IgM in *E. coli*, where the light and heavy fragments are cloned into an expression vector and the light chain is fused to MalE (maltose binding protein) signal sequence of E. coli and the heavy chain variable region and first constant region are fused to the alkaline phosphatase signal sequence of *E. coli,* culturing the transformed cell and isolating and purifying the immunoglobulin constant domain in the form of a Fab fragment.

14. Claims 1-4, 6-8 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002).

The interpretation of Claims 1-4, 6-8 and 14 is discussed supra.

Capon discloses methods for producing immunoadhesons comprising an Ig light and/or heavy chain constant region [0025] and signal sequence fusions in order to more expeditiously direct the secretion of the Ig fusion molecule, where the nucleotides encoding the Ig constant regions and E. coli signal peptide are expressed in E. coli [0069]. The heterologous signal replaces the native adheson signal, and when the resulting fusion is recognized, i.e. processed and cleaved by the host cell, the adheson is secreted. Signals are selected based on the intended host cell, and may include bacterial sequences [0023]. The Ig constant region is selected for retaining at least a functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain [0026] and suitable immunoglobulin Ig constant domains are obtained from IgG-1, -2, -3, or -4 subtypes, IgA, IgE, IgD or IgM, and preferably IgG-1 [0038]. Capon discloses E. coli transformants expressing nucleotides encoding the Ig constant region and signal peptide [0069].

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 1-8, 10 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al. (WO 01/03737; published 1/19/01) in view of Adib-Conquy et al. (Protein Engineering 8:859-863 (1995); cited in the PTO 892 form of 8/7/07).

The interpretation of Claims 1-8, 10 and 14 is discussed supra.

The method of producing an Ig constant region from a prokaryotic cell transformed with an expression vector encoding a nucleotide encoding an Ig constant region and a nucleotide sequence encoding an E. coli-derived signal sequence was prima facie obvious over Cox and Adib-Conquy.

Cox discloses methods for expressing and purifying Ig fusion proteins from expression vectors comprising the Fc domain of antibodies and a signal sequence from a transformed host cell such as a bacterium (p. 9, lines 24-34), where the Ig domains

include IgG-Fc, IgG-CH, an Fc or CH domain from another class, i.e., IgM, IgA, IgE, IgD or a light chain constant domain (p. 7, lines 35-38), examples of IgG4 gene fusions (Example 1), hinge regions included in the Ig constant domain (p. 8, lines 1-3), aglycosylated forms (e.g., "changes in carbohydrate...or other attached groups found on natural proteins" (p. 9, lines 13-15)). Cox appreciates signal peptides required for expression of the Ig constant region (see Example 1, EPO signal sequence) and expressing the proteins in bacteria, but does not specifically teach an E. coli signal peptide, which Adib-Conquy rectifies in its disclsoure.

The interpretation of Adib-Conquy is discussed supra.

One skilled in the art at the time of the invention would have been motivated to have produced the instant method and been reasonably assured of success based on the combined disclosures of Cox and Adib-Conquy. Both Cox and Adib-Conquy specifically teach expressing proteins comprising Ig constant regions and signal peptides encoded by nucleotides from prokaryotic cells and purifying the protein from the transfected host cell. Cox teaches that the Ig constant region can comprise less than the full constant region from IgG1-4 or IgA, IgE, IgM and IgD and even glycosylation-modified forms of Igs so long as they remain as functional domains, and where the nucleic acids encoding the Ig constant domain or signal peptide are expressed in bacteria. One skilled in the art could have readily modified the method of Cox and been assured of success in view of Adib-Conquy to express both light and heavy chain constant domains in-frame with E. coli derived signal sequences, specifically alkaline phosphatase and MelB, to express a molecule comprising an Ig

constant domain in a transformed prokaryotic cell because Adib-Conquy had already accomplished expressing an IgM Fab fragment in E. coli. The method was prima facie obvious over Cox and Adib-Conquy for all of the foregoing reasons.

16. Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) in view of Sun et al. (USPN 6797493; published 9/28/04; filed 10/1/01).

The interpretation of Claim 1 is discussed supra. Claim 9 is drawn to the method where the Ig constant region is represented by amino acid sequence of SEQ ID NO:29.

The method claims for producing an Ig constant region from a prokaryotic cell transformed with a nucleotide encoding an Ig constant region of SEQ ID NO: 29 and an E. coli-derived signal peptide was prima facie obvious at the time of the invention over Capon and Sun.

The interpretation of Capon is discussed supra.

Sun discloses a method for making a recombinant fusion protein comprising hG-CSF and a human IgG Fc variant and more specifically, comprising an IgG4 constant domain of SEQ ID NO:29 (see attached sequence search alignment with the peptide sequence of SEQ ID NO:29).

One skilled in the art at the time of the invention would have been motivated to have produced and been reasonably assured of success in having produced the instant claimed method over Capon and Sun. Capon and Sun both expressly teach generating recombinant Ig constant regions especially IgG4 CH regions based on recombinant

techniques. Where Capon discloses using E. coli as host expression systems transformed with nucleotides encoding the IgG4 constant region and E. coli derived signal peptides, one skilled in the art would have been motivated and been assured of success in modifying the method of Capon by introducing the IgG4 constant region of Sun because both references were successful in demonstrating the expression of IgG4 isoforms, and the technology to modify the nucleotide of Capon with the nucleotide encoding SEQ ID NO:29 was well within the reach and understanding of one of ordinary skill in the art at the time of the invention. For all of the foregoing reasons, the method was prima facie obvious over Capon and Sun.

17. Claims 1, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) in view of Reilly et al. (US20050048572; published March 3, 2005; filed 10/30/03).

The interpretation of Claims 1 and 10 is discussed supra. Claim 10 is further drawn to where the signal peptide is penicillinase, lpp, heat-stable enterotoxin II, LamB, PhoE, PelB, and OmpA, and Claim 11 is drawn to the heat stable enterotoxin signal peptide of SEQ ID NO: 36.

The method claims for producing an Ig constant region from a prokaryotic cell transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide was prima facie obvious at the time of the invention over Capon and Reilly.

The interpretation of Capon is discussed supra.

Reilly discloses methods of expressing Fc fusion proteins from expression plasmids encoding Fc portions of heavy and light chains from transformed E. coli [0285], where the a recombinant vector comprises a secretion signal sequence component for prokaryotic host cells that do not recognize and process the signal sequences native to the heterologous polypeptides, and the signal sequence is substituted by a prokaryotic signal sequence such as alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II (STII) leaders, LamB, PhoE, PelB, OmpA and MBP. Reilly teaches that the signal sequences used in both cistrons of the expression system are STII signal sequences or variants thereof [0122]. Reilly teaches using "the heat-stable enterotoxin II signal sequence (STII) (Picken et al., Infect. Immun. 42:269-275, 1983, and Lee et al., Infect. Immun. 42:264-268, 1983) for the periplasmic secretion of heavy and light chains, and fine control of translation for both chains was achieved with previously described STII signal sequence variants of measured relative translational strengths, which contain silent codon changes in the translation initiation region (TIR) (Simmons and Yansura, Nature Biotechnol. 14:629-634, 1996; Simmons et al., J. Immunol. Methods (2002) 263:133-147)" [0216]. Applicants specification teaches that the native heat-stable enterotoxin (STII) has the sequence of SEQ ID NO:36 (p. 18, lines 8-11), thus by incorporation through reference to Simmons and Yansura (see Table 1, WT SII nucleotide sequence), Reilly teaches the wt heat-stable enterotoxin signal peptide corresponding to SEQ ID NO: 36.

One skilled in the art at the time of the invention would have been motivated to have produced and been reasonably assured of success in having produced the

method invention based on the combined disclosure of Capon and Reilly. Both Capon and Reilly expressly teach methods using transformed prokaryotic cells to express an Ig constant region where the transformant is transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide and culturing the cells to express for purification the Ig constant region. Both Capon and Reilly expressly teach bacterial signal sequences, where Reilly more specifically teaches using the E. coli-derived signal sequences alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II (STII) leaders, LamB, PhoE, PelB, OmpA and MBP, and more specifically, the wt heat-stable enterotoxin signal peptide of SEQ ID NO:36. Because each of the references appreciates and teaches signal peptides as being critical to the respective host and bacterial signal peptides had been shown by both references to enable the expression of heavy and light chain constant regions in transformed E. coli, one skilled in the art would have found more than sufficient motivation and been reasonably assured of success in having introduced the E. coli-derived signal peptide sequences of Reilly into the method of Capon in order to arrive at the objective of the instant claimed method. For all of the foregoing reasons, the method was prima facie obvious over Capon and Reilly.

18. Claims 1, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) in view of Reilly et al. (US20050048572; published March 3, 2005; filed 10/30/03) as

applied to claims 1 and 10 above, and further in view of Kwon et al. (USPN 6605697; published 8/12/03; filed 6/14/01).

The interpretation of Claims 1 and 10 is discussed supra. Claim 11 is drawn to the heat stable enterotoxin signal peptide of SEQ ID NOS: 36-46.

The method claims for producing an Ig constant region from a prokaryotic cell transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide comprising a heat-stable enterotoxin signal peptide was prima facie obvious at the time of the invention over Capon and Reilly in view of Kwon.

The interpretation of Capon and Reilly is discussed supra.

Kwon discloses expression of fusion proteins in prokaryotic cells where the fusion protein is encoded by a sequence comprising a bacterial-derived signal peptide, and more especially the heat stable enterotoxin peptides (STII) corresponding to SEQ ID NOS:36-46 of Claim 11 are disclosed. See SEQ ID NOS: 1 and 13-22 of Kwon (Table 2). Kwon teaches that the yield of secreted heterologous protein decreases as the secretory efficiency of the signal peptide becomes low. Therefore, the yield of secreted heterologous proteins may be enhanced by modifying the signal peptide moiety of fusion proteins expressed in host microorganisms.

One skilled in the art at the time of the invention would have been motivated to have produced and been reasonably assured of success in having produced the method invention based on the combined disclosure of Capon, Reilly and Kwon. Both Capon and Reilly expressly teach methods using transformed prokaryotic cells to express an Ig constant region where the transformant is transformed with a nucleotide

encoding an Ig constant region and an E. coli-derived signal peptide and culturing the cells to express for purification the Ig constant region. Both Capon and Reilly expressly teach bacterial signal sequences, where Reilly more specifically teaches using the E. coli-derived signal sequences alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II (STII) leaders, LamB, PhoE, PelB, OmpA and MBP, and more specifically, the wt heat-stable enterotoxin signal peptide of SEQ ID NO:36. Kwon also teaches using the signal sequence of SEQ ID NO:36 for the wild type heat stable enterotoxin II signal peptide and variants thereof in order to express heterologous fusion proteins in E. coli expression systems. Further because Kwon appreciates the sensitivity of the signal peptide sequence in achieving the stability, e.g., expression of the full length fusion protein in a prokaryotic system and provides examples that are shown to work using various fusion proteins, one skilled in the art would have found more than sufficient motivation to have introduced the heat stable enterotoxin signal peptides of Reilly and Kwon into the method of Capon and Reilly in order to reliably and reproducibly express an Ig constant region from a prokaryotic system. Because each of the references appreciates and teaches bacterial signal peptides as being critical to the respective host, and bacterial signal peptides had been shown by all of the references to enable the expression of fusion proteins, where Capon and Reilly further demonstrate expression of heavy and light chain constant regions in transformed E. coli, one skilled in the art would have found more than sufficient motivation and been reasonably assured of success in having introduced the E. coli-derived signal peptide sequences of Reilly and kwon into the method of Capon in order to arrive at the objective of the

instant claimed method. For all of the foregoing reasons, the method was prima facie obvious over Capon and Reilly and Kwon.

***Conclusion***

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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